LESSONS FROM PREVENTIVE INFECTIOUS DISEASE VACCINES

DEVELOPMENT OF THERAPEUTIC CANCER VACCINES

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LESSONS FROM PREVENTIVE VACCINES

- Vaccine Development Overview
- Product and QC Issues
- Pre-Clinical/Non-Clinical Studies
- Clinical Considerations

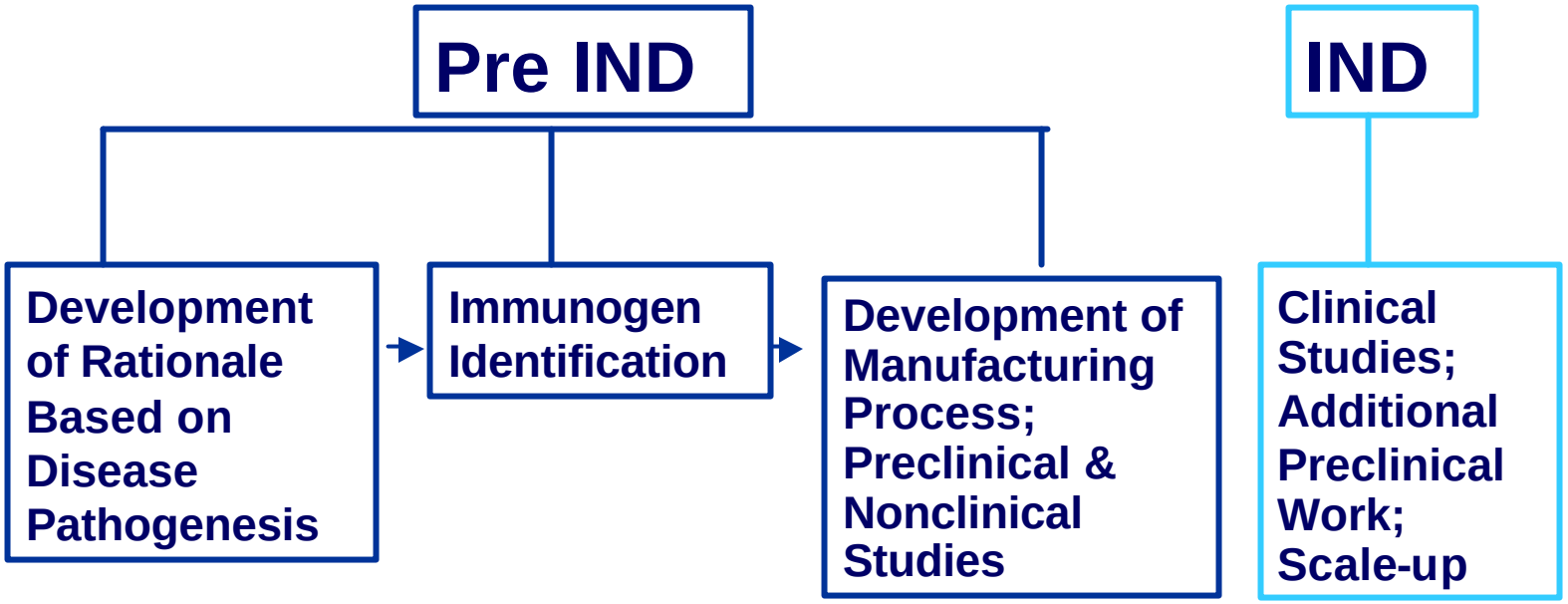
Vaccines For Infectious Disease Indications

- Reviewed by OVRR, CBER.
- Preparation consisting of all or a portion of a disease-causing organism or the nucleic acid encoding one or more of the proteins from that organism, which is intended to induce an immune response to the vaccine for the prevention or treatment of the disease or condition.

Types of Preventive Vaccines

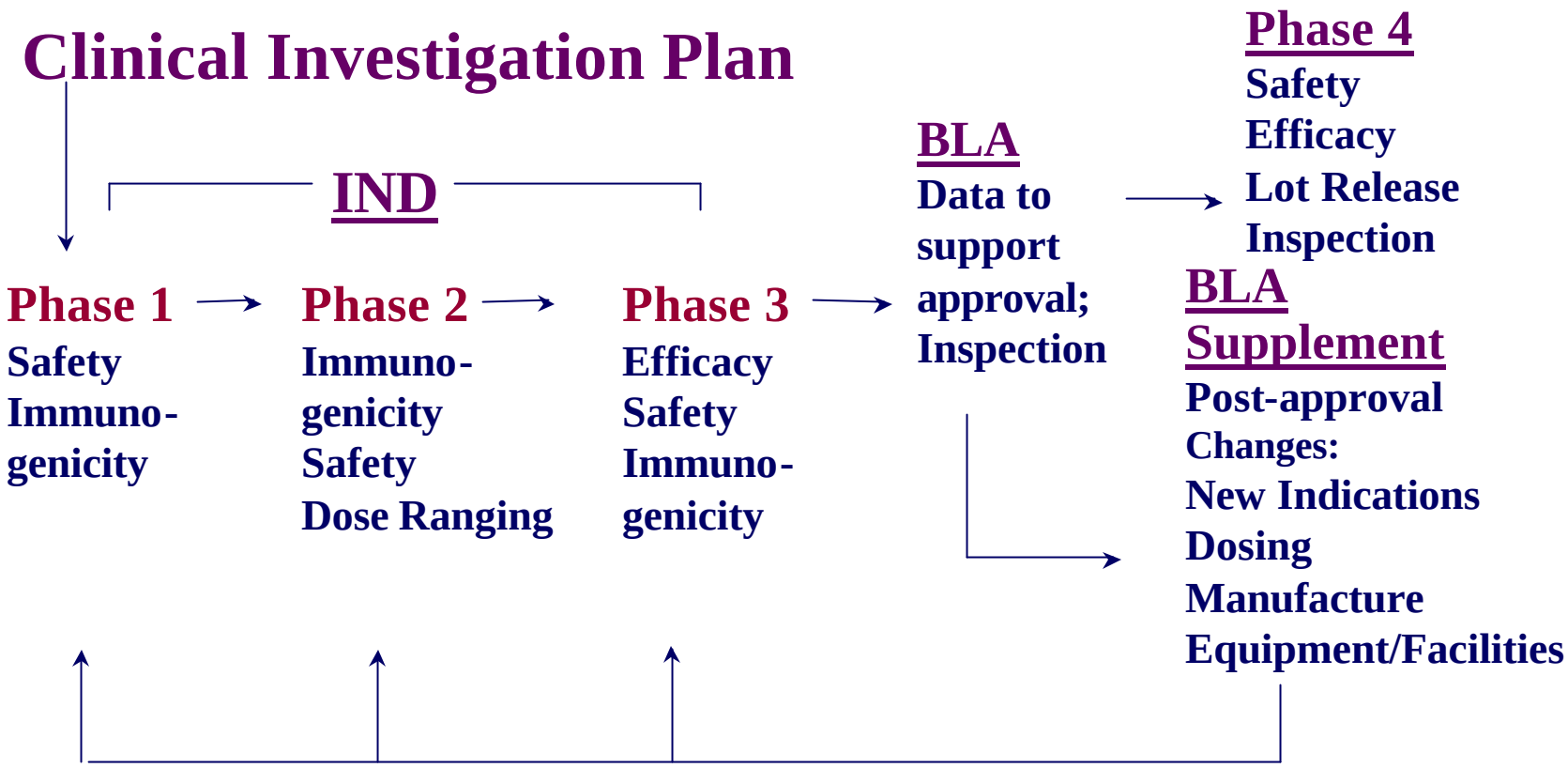
- **Live, attenuated:** MMR, OPV, Varicella, YF, Salmonella Ty21A
- **Inactivated:** HAV, influenza, IPV, rabies
- **Crude or purified antigens** derived from living or killed cells: diphtheria and tetanus toxoids, acellular pertussis antigens, polysaccharides
- **Conjugate vaccines:** Hib and pneumococcal PS-Protein conjugate
- **Recombinant DNA derived:** Hepatitis B Vaccine
- **Vectored and DNA vaccines** (investigational)

Vaccine Development



IND =Investigational New Drug application

Stages of Review and Regulation



IND = Investigational New Drug Application; BLA=Biologics License Application

- PRODUCT & QC CONSIDERATIONS

Licensed biological products, including vaccines, must be:

- **Safe:** “relatively free from harmful effect when prudently administered”
- **Pure:** “relatively free from extraneous matter”
- **Potent:** “specific ability of product … to effect a given result”
- Manufactured consistently according to current Good Manufacturing Practices

Vaccine Production and Quality Control: Common Principles

- Detailed manufacturing procedures: consistency of production
- Defined compatible components
- Product characterization: specifications
- Adventitious agent testing
- Examination for extraneous materials
- Stability, including genetic stability

Vaccine Production

- Source and quality of starting materials
- Selection/characterization of cell substrate, e.g., history, identity, endogenous viruses, adventitious agents
- Viral or bacterial seed history and characterization
- Cell banks: bacterial, viral, cell substrates

Vaccine Production (2)

- Validation of manufacturing process for removal and/or inactivation of viruses or bacteria
- In process testing
- Release testing of bulk and final products
- Stability testing of final product, bulk, critical intermediates

Tests for Specific Virus Contaminants in Cell Substrates

For Example:

- Human derived: EBV, CMV, Hep B and C, human herpes viruses
- Simian derived: Simian herpes viruses, simian CMV, adenovirus, SV-40, SV-5, simian retroviruses
- Rodent derived: LCM and others

Lot Release Testing

- **Sterility – bacterial or fungal contaminants**
- **General safety test - guinea pigs and mice to detect extraneous toxic contaminants**
- **Identity test - e.g., SDS-PAGE, Western blot, immunologic assay or amino acid analysis**
- **Purity - e.g., % moisture, SDS-PAGE, HPLC, endotoxin**
- **Potency - in vivo or in vitro test to assess immunogenicity, antigen content, or chemical composition**
- **Tests for removal of process contaminants**

- PRECLINICAL & NONCLINICAL STUDIES

VACCINE PRECLINICAL STUDIES

- Product Characterization
- Attenuation (Live Organisms)
- Inactivation/Reversion
- Absence of Adventitious Agents
- Pyrogenicity
- Potency, Immunogenicity
- Challenge/Protection Studies
- GLP toxicity study (novel products)

Preclinical Safety Studies

- Study design predicated on intended clinical use
- Relevant animal model
  - Vaccine immunogenic in chosen species
  - Non-human primates usually not necessary
- Minimize animal use by combining safety and immunogenicity evaluations
- Evaluation of product specific concerns
- Reproductive toxicity studies (prior to study specifically enrolling pregnant women)
- Safety studies conducted under GLP requirements

Adjuvants

- **Adjuvant - An agent that enhances specific immune responses to antigens.**
- **To date, aluminum compounds are the only adjuvants included in currently licensed vaccines.**
- **Specific vaccine/adjuvant formulation is licensed, vs. adjuvant alone.**
- **Need for adjuvant should be justified with clinical safety and immunogenicity data (21 CFR 610.15a).**

- CLINICAL CONSIDERATIONS

Stages of Review and Regulation

- **Investigational New Drug Application**
  - **Phase 1: safety, immunogenicity**
  - **Phase 2: safety, immunogenicity, dose ranging**
  - **Phase 3: efficacy, safety, immunogenicity**

Stages of Review and Regulation (2)

- Biologics License Application
  - Review of data to support licensure
  - Pre-approval inspection
  - Advisory Committee (VRBPAC)
- Post-licensure
  - Phase 4 studies
  - VAERS (passive surveillance)
  - Lot release
  - Biennial inspections

Phase 1 Clinical Trials

- Initial use of investigational vaccine
- Limited # of subjects, e.g., 20 in a trial
- Closely monitored
  - Consider vaccine-specific issues, e.g. for live vaccines, shedding, risk of transmission
- Often open label (may depend on experience with similar products)
- Population - Inclusion/exclusion criteria
- Typically evaluate healthy adults in first trial

Phase 2 Clinical Trials

- Often randomized & controlled
- Include study participants representative of those to be enrolled in Phase 3 trials
- Further characterize safety, vaccine-elicited immune response
- Determine dose(s) to be used in Phase 3
- Evaluate potential for immune interference with other concurrently administered vaccines (often done as a separate study)
- Pilot disease case definition for efficacy trial

Phase 3 Clinical Trials (Efficacy)

- Typically double-blinded, randomized, controlled
- Background epidemiology essential for sample size calculation
- Case definition
  - Well-defined clinical criteria and validated assays for laboratory diagnosis (culture, serology, etc.)
  - Clinical relevance

Phase 3 Trials (2)

- Prospective primary and secondary endpoints
- Monitoring
  - Case surveillance
  - Safety
  - Duration
  - Immunogenicity and correlates of protection
  - Data Monitoring Committee
- Data analysis plan

Clinical Studies: Safety Evaluation

- Definition of safety (FDA, 21 CFR 600.3).
  - **“relative freedom from harmful effect to persons affected directly or indirectly by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.”**
- **Risk/Benefit: generally for use in <u>healthy persons.</u>**

FDA Guidance to Industry - Providing Clinical Evidence of Effectiveness (1998)

- For human drugs and biological products
  - Two efficacy trials are the “standard”
  - One trial can be adequate if result compelling, which is often the case for vaccine efficacy trials with clinical disease endpoints
    - »e.g., robust data, multicenter trial

IMMUNOGENICITY

- **The ability to induce an immune response:**
  - **Humoral or antibody**
  - **Cell-mediated**
- **Factors that affect immunogenicity:**
  - **Maternal Ab, nature & dose of vaccine, route of administration, adjuvant, host factors (age, nutritional status, genetics, coexisting disease)**

IMMUNOGENICITY (2)

- Typical results reported & analyzed:
  - Percent Responders
  - Geometric Mean Titers (GMT)
  - Reverse Cumulative Distribution Curves (RCDC)
- Functional antibody assays (e.g., neutralizing) may be needed in addition to binding alone (e.g., ELISA)
- Assay validation critical

Correlate of Protection

- **A predictor of vaccine efficacy based on a particular type and quantity of immune response associated with protection from disease or infection.**
- **Allows an assessment of protection for an immunized individual.**

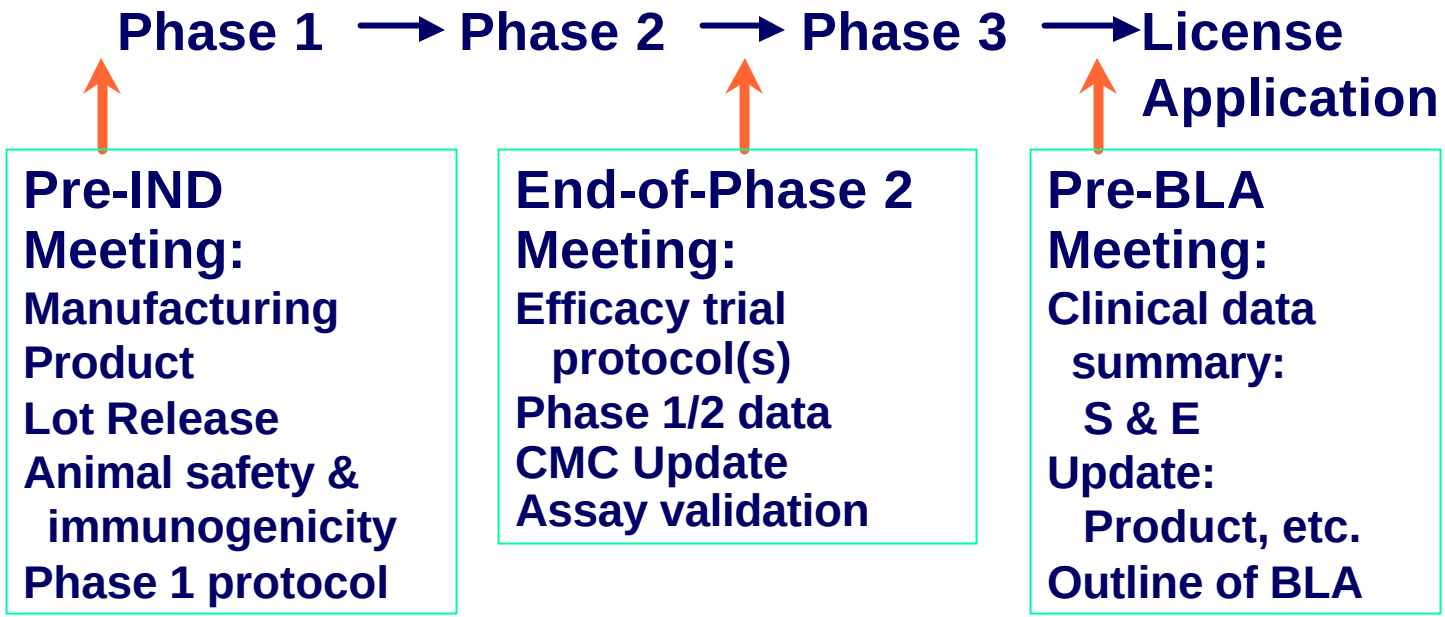
Correlate of Protection (2)

- An immune correlate of protection may be identified from successful efficacy trial.
- May also be suggested from other sources, e.g., post-infection immunity.
- Correlate of protection useful for interpreting immune response data, e.g., “bridging studies.”
- Inability to find a correlate from successful efficacy trial does not preclude licensure.

Preventive Vaccine Clinical Studies: Other Considerations

- Simultaneous administration with other vaccines (infants, travelers, military)
- Safety of extra doses of vaccine antigens
- Bridging studies
  - Manufacturing change, different population, new dosing schedule
- Clinical lot consistency studies
- Combination vaccines

Meetings with FDA
(21 CFR 312.47)



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US Code of Federal Regulations

- 21 CFR 50 - Protection of Human Subjects
- 21 CFR 56 - Institutional Review Boards
- 21 CFR 58 - Good Laboratory Practices
- 21 CFR 210, 211 - Good Manufacturing Practices
- 21 CFR 312 - Investigational New Drug Applications (INDs)
- 21 CFR 314.126 - Adequate and Well-Controlled Trials
- 21 CFR 610 - General Biological Product Standards

Available Resources

- FDA documents /Federal Register (FR) notices /FDA regulations
  - http://www.fda.gov/cber/publications.htm
  - 1-800-835-4709 or 301-827-1800
  - OCTMA@CBER.FDA.GOV (Consumer Questions)
  - MATT@CBER.FDA.GOV (Manufacturers Assistance)
- International Conference on Harmonisation (ICH) Documents (U.S., E.U. and Japan)
- Parkman P, Hardegree MC: Regulation & Testing of Vaccines. Vaccines 3rd ed, 1999, WB Saunders
- Chandler D, McVittie L, Novak J: IND Submissions for Vaccines. Vaccines: From Concept to Clinic 1999, CRC Press

Vaccine Development: Conclusions

- Preventive Vaccines have unique considerations for product & clinical development
- Overall planning and coordination:
  - Product characterization & manufacturing (cGMP)
  - Anticipate needs of future trials, e.g., critical assays
  - Accumulate sufficient safety, immunogenicity & efficacy data during development
  - Clinical bridging studies, e.g., population; scale-up
  - Prospective application of Good Clinical Practices
- Utilize available FDA documents/resources

- BACKUP SLIDES

Clinical Studies: Safety Evaluation (cont.)

- Thus, safety is relative and risk tolerance may be influenced by:
  - **Risk of vaccine-preventable disease vs. risk of adverse event associated with vaccine**
    - » **these risks may change over time**
  - **Alternative treatments (e.g., other vaccines)**
    - » **e.g., recommendation for use of IPV instead of OPV**
  - **Intended population**

Review of a BLA and Post-licensure Activities

- Multi-disciplinary review (microbiologists, chemists, toxicologists, medical officers, statisticians, etc.) of the product, manufacturing, clinical data
- Advice usually sought from FDA's VRBPAC
- Labeling must be supported by the data
- Phase 4 commitments may be requested at time of licensure
- Post licensure, monitoring of the products continues through lot release, VAERS, and biennial inspections

Usual Timelines for Review

- IND: original submission reviewed within 30 days of receipt, study may proceed at 30 days unless placed on clinical hold by FDA
- IND amendments: new protocols may proceed immediately, although FDA strongly encourages end-of-phase 2 and pre-BLA meetings; an IND can be placed on hold at any time for safety reasons or for clinical design issues for phase 2 or 3 studies
- BLA: standard review completed within 10 months, priority review within 6 months

Guidance Documents - Examples

- FDA Guidance for Industry
  - Content and Format of Chemistry, Manufacturing Controls Information and Establishment Description Information for a Vaccine or Related Product (1999)
- ICH Guidance Documents
  - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (1998)
  - Quality of Biological Products: Derivation and Characterization of Cell Substrates (1998)

Design of Preclinical Studies to Assess Vaccine Efficacy

- Challenge/protection studies
  - Provides rationale for use in humans
  - Determination of optimal dose
- Pathogen should replicate in chosen model
  - HSV in guinea pigs, influenza in ferrets, RSV in cotton rats, SIV/SHIV in macaques